Layered hydrogels accelerate iPSC-derived neuronal maturation and reveal migration defects caused by MeCP2 dysfunction.

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Public Summary:
In this work, we generated a novel method to grow neural cells derived from patients that resemble the tridimensional architecture of the human brain. Our results showed that the new technology helps to speed it up neuronal maturation in vitro and to identify novel phenotypes that were masked by current two-dimensional cultures.

Scientific Abstract:
Probing a wide range of cellular phenotypes in neurodevelopmental disorders using patient-derived neural progenitor cells (NPCs) can be facilitated by 3D assays, as 2D systems cannot entirely recapitulate the arrangement of cells in the brain. Here, we developed a previously unidentified 3D migration and differentiation assay in layered hydrogels to examine how these processes are affected in neurodevelopmental disorders, such as Rett syndrome. Our soft 3D system mimics the brain environment and accelerates maturation of neurons from human induced pluripotent stem cell (iPSC)-derived NPCs, yielding electrophysiologically active neurons within just 3 wk. Using this platform, we revealed a genotype-specific effect of methyl-CpG-binding protein-2 (MeCP2) dysfunction on iPSC-derived neuronal migration and maturation (reduced neurite outgrowth and fewer synapses) in 3D layered hydrogels. Thus, this 3D system expands the range of neural phenotypes that can be studied in vitro to include those influenced by physical and mechanical stimuli or requiring specific arrangements of multiple cell types.